PB88-180229

Health Effects Assessment for Alpha- and Beta-Endosulfan

(U.S.) Environmental Protection Agency
Cincinnati, OH

May 87

U.S. Department of Commerce
National Technical Information Service
NTIS

PB88-180229

EPA/600/8-88/034
May, 1987

HEALTH EFFECTS ASSESSMENT FOR ALPHA- AND BETA-ENDOSULFAN

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA/600/8-88/034	2.
3. RECIPIENT'S ACCESSION NO. PB88 180229/AS	
4. TITLE AND SUBTITLE Health Effects Assessment for alpha- and beta-Endosulfan	5. REPORT DATE May 1987
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 39
	20. SECURITY CLASS (This page) Unclassified	22. PRICE PC A03/MF A01

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with α- and β-endosulfan. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/ DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Endosulfan. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-046. NTIS PB81-117574.

U.S. EPA. 1986a. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Endosulfan. Online (verification date 6/11/86; data input pending). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

An RfD_{SO} of 0.01 mg/day was calculated for endosulfan from a LOAEL for nephrctoxicity in rats in a 2-generation reproduction study (Huntingdon Research Centre, 1984). An RfD_0 of 0.001 mg/day was calculated from the same study. Mice appeared to be more sensitive than rats or dogs to the effects of endosulfan. A CS of 50 based on mortality in mice was calculated from a 73-week oral study.

Data were not available for inhalation toxicity of endosulfan. The oral studies in rats and mice are inadequate to clearly assess the carcinogenic potential of endosulfan.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and John Helms (Office of Toxic Substances) was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

Editorial review for the document series was provided by the following:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by the following:

Bette Zwayer, Jacky Bohanon and Kim Davidson
Environmental Criteria and Assessment Office
Cincinnati, OH

TABLE OF CONTENTS

		Page
1.	ENVIRONMENTAL FATE AND TRANSPORT	1
2.	ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS	3
2.1.	ORAL	3
2.2.	INHALATION	3
3.	TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS	4
3.1.	SUBCHRONIC	4
3.1.1.	Oral	4
3.1.2.	Inhalation	6
3.2.	CHRONIC	6
3.2.1.	Oral	6
3.2.2.	Inhalation	9
3.3.	TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS	9
3.3.1.	Oral	9
3.3.2.	Inhalation	11
3.4.	TOXICANT INTERACTIONS	11
4.	CARCINOGENICITY	12
4.1.	HUMAN DATA	12
4.2.	BIOASSAYS	12
4.2.1.	Oral	12
4.2.2.	Inhalation	13
4.3.	OTHER RELEVANT DATA	13
4.4.	WEIGHT OF EVIDENCE	14
5.	REGULATORY STANDARDS AND CRITERIA	15
6.	RISK ASSESSMENT	16
6.1.	SUBCHRONIC REFERENCE DOSE (RfD_S)	16
6.1.1.	Oral (RfD_{SO})	16
6.1.2.	Inhalation (RfD_{SI})	17

TABLE OF CONTENTS (cont.)

	Page
6.2. REFERENCE DOSE (RfD)	17
6.2.1. Oral (RfD_O)	17
6.2.2. Inhalation (RfD_I)	20
7. REFERENCES	21
APPENDIX	28

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CNS	Central nervous system
CS	Composite score
DMSO	Dimethyl sulfoxide
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MED	Minimum effective dose
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties and environmental fate of α- and β-endosulfan are listed in Table 1-1.

Endosulfan sulfate is a potential major transformation product of α- and β-endosulfan in water and soil (Callahan et al., 1979; Sanborn et al., 1977). The dominant pathways for removal of α- and β-endosulfan from water at pH <7 are not known. The estimated oxidation half-life for the isomers in water is 70 days at 20°C, and the estimated hydrolysis at pH 5.5, 7 and 8 is 170, 35 and 3.5 days, respectively (Callahan et al., 1979). The hydrolysis half-life of endosulfan at 30°C varies from 0.5 hours to 90 days in the pH range of 9.0-4.5 (Singh et al., 1986). Therefore, hydrolysis is important in waters at pH >7. The α- and β-endosulfan isomers should strongly adsorb to soil and remain primarily within the upper few centimeters. Technical endosulfan is ≥95% pure and is composed of two stereoisomers, α- and β-endosulfan (U.S. EPA, 1980a). The technical product consists of ~70% α-endosulfan and ~30% β-endosulfan.

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives
for α- and B-Endosulfan

Property	Value	Reference
CAS number:	α-: 959-98-8 B-: 33213-65-4	
Chemical class:	chloroorganic pesticide	
Molecular weight:	406.95	
Melting point:	α-: 108-110°C B-: 207-209°C	Callahan et al., 1979
Vapor pressure:	α- and B- mixture: $1x10^{-5}$ mm Hg at 25°C	Callahan et al., 1979
Water solubility:	α-: 0.32 mg/ℓ at 20°C B-: 0.33 mg/ℓ at 20°C	Worthing, 1983
Log octanol/water partition coefficient:	α-: 3.83	Hansch and Leo, 1985
Bioconcentration factor:	α-: 17-999 (algae) 1336-5763 (snail) 30-304 (fish)	Callahan et al., 1979
	B-: 44-3863 (algae) 8174-39,457 (snail) 90 and 388 (fish)	Callahan et al., 1979
Soil adsorption coefficient:	Technical grade: 328-2755 (fish)	U.S. EPA, 1980a
	α- and B-: 2900 (estimated)	Lyman et al., 1982
Half-lives in water:	<1-170 days (dependent on pH)	Callahan et al., 1979; Singh et al., 1986
Half-lives in soil:	α-: 60 days B-: 800 days	Sanborn et al., 1977

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

The α- and β- isomers of [^{14}C]-endosulfan were administered to rats separately as single 2 mg/kg oral doses in corn oil (Dorough et al., 1978). No appreciable differences were observed in the fecal (or urine) elimination of radioactivity of the two isomers. Approximately 11 and 13%, 55 and 62% and 68 and 75% of the administered radioactivity was eliminated in the feces at 24, 48 and 120 hours after treatment with the α- and β- isomers, respectively. Analyses of bile collected for 48 hours showed that ~47% of the α-endosulfan dose and 29% of the β-endosulfan dose was eliminated by this route. Enterohepatic circulation was not demonstrated, since bile duct cannulation did not alter the amount of radioactivity excreted into the urine. These data and the results of bile duct cannulation experiments at 48 hours suggest that gastrointestinal absorption of endosulfan was on the order of 40%.

Maier-Bode (1968) indicated that undiluted endosulfan is slowly and incompletely absorbed from the mammalian gastrointestinal tract. Further information was not provided.

2.2. INHALATION

Pertinent data regarding the absorption of α- or β-endosulfan following inhalation exposure could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

Toxicity studies of endosulfan typically evaluated the technical grade products, which are mixtures of the α- and β- isomers.

3.1. SUBCHRONIC

3.1.1. Oral. Gupta and Gupta (1977) administered daily gavage doses of 0, 1.0, 2.5 and 5.0 mg/kg to rats for 7-15 days. At the 2.5 and 5.0 mg/kg/day levels, relative liver weight increased and pentobarbitol-induced sleeping time decreased, indicating possible induction of hepatic microsomal enzymes; however, no effects on organ weights or sleeping time occurred at 1 mg/kg/day. In another experiment, Den Tonkelaar and van Esch (1974) determined NOELs for induction of various liver microsomal enzymes in male rats. For endosulfan, the NOEL and LOEL for induction were 50 and 200 ppm in the diet administered for 2 weeks. The authors stated that this value agrees with a NOEL of 50 ppm for histopathological liver abnormalities in a long-term experiment from an unspecified unpublished report. Assuming a rat consumes food equivalent to 5% of its body weight/day (U.S. EPA, 1980b), the NOEL and LOEL are 2.5 and 10 mg/kg/day, respectively.

Female rats administered a diet containing 50 ppm (2.5 mg/kg/day) for 28 days exhibited no effects on body weight gain, relative liver or kidney weights or induction of liver microsomal oxidase enzymes (Dorough et al., 1978). Oral administration of 2.5 or 7.5 mg/kg/day for 60 days resulted in increased relative liver and lung weights in male rats (Ansari et al., 1984). In another study, rats given oral dosages of 5 mg/kg/day for 30 days showed signs of toxicity (hyperexcitability, tremor, dyspnea and salivation), which disappeared after 3-4 days; however, there were no changes in relative organ weights or biochemical, limited histological, hematological

and fertility parameters (Dikshith et al., 1984). These authors also reported NOELs of 0.75 and 2.5 mg/kg/day in males and 0.25 and 0.75 mg/kg/day in females. ACGIH (1986) reported that rats tolerated oral doses up to 3.2 mg/kg/day for ? months without injury, but additional information regarding this study (Czech, 1958) was not reported.

NCI (1978) conducted preliminary subchronic studies in which groups of five male and five female Osborne-Mendel rats and five male and five female B6C3F1 mice were exposed for 6 weeks to the following endosulfan concentrations in the diet: rats - 0, 178, 316, 562, 1000 and 1780 ppm; mice - 0, 3.2, 5.6, 10, 18 and 32 ppm. The animals were observed for an additional 2 weeks. In male rats, body weights were depressed 9% at 562 ppm and 10% at 1000 ppm. In male and female mice, body weights were depressed at $\geq$5.6 ppm. One female died at 5.6 ppm, one male died at 10 ppm and, at the higher concentrations, mortality increased in both sexes of mice with increasing dosage. In rats, dose-related body weight depression occurred in males only at concentrations $\geq$562 ppm; deaths occurred in males at 1780 ppm and females at 316 and 562 ppm, but mortality did not appear to be dose-related. Indices other than body weight and mortality were not evaluated. If it is assumed that rats and mice consume food equivalent to 5 and 13% of their body weight in food/day, respectively (U.S. EPA, 1980b), the rat 178 ppm NOEL reflects 8.9 mg/kg/day dosage and the mouse 3.2 ppm NOEL reflects 0.4 mg/kg/day dosage.

U.S. EPA (1982) summarized several unpublished Hazleton Laboratories and FMC Corp. studies, which appear to be the same as those described briefly by Maier-Bode (1968), ACGIH (1986) and Vettorazzi (1975). One of these was a subchronic study by Baran (1967), in which groups of four male and four female beagle dogs were fed diets containing 0, 3, 10 or 30 ppm technical

grade endosulfan for 2 years. One male and one female from each group were sacrificed after 1 year and the remaining dogs at the end of the experiment. No treatment-related effects on gross pathology, histopathology, hematology, clinical chemistry or urine chemistry were observed. If it is assumed that a dog consumes an amount of food equivalent to 2.5% of its body weight/day (U.S. EPA, 1986b), the 30 ppm NOEL is equivalent to 0.75 mg/kg/day. The U.S. EPA (1982) evaluation of this study concluded that it was deficient because it did not report food consumption, body weight and organ weight data. There were also some discrepancies in the data (for example, leucocyte counts at 18 and 21 months were reported for a dog that supposedly died after 15 months). In another subchronic dog study (Keller, 1959a) described by U.S. EPA (1982), groups of mongrel dogs were given endosulfan in gelatin capsules at dosages of 0, 0.075, 0.25 or 0.75 mg/kg/day, 6 days/week for 1 year. No effects on growth, organ weight, biochemical and hematological parameters or urine chemistry were observed, and there were no differences in gross pathology or histopathology between treated dogs and controls. The NOEL of 0.75 mg/kg/day in this study is equivalent to the 30 ppm dietary NOEL of Baran (1967). U.S. EPA (1982) concluded that this was an adequate subchronic oral study in dogs.

3.1.2. Inhalation. Pertinent data regarding the toxic effects of subchronic inhalation were not located in the available literature.

3.2. CHRONIC

3.2.1. Oral. An NCI (1978) carcinogenesis bioassay was conducted in which technical grade endosulfan (98.8% pure) was administered in the diets of Osborne-Mendel rats and B6C3F1 mice. Groups of 50 animals/sex/species received the endosulfan-containing diets for 78 weeks, followed by an observation period of 14 weeks for mice or 33 weeks for rats. Groups of 20

animals/sex/species served as matched controls. The TWA endosulfan concentrations in the diet were as follows: male rats, 408 or 952 ppm; female rats, 223 or 445 ppm; male mice, 3.5 or 6.9 ppm; and female mice, 2.0 or 3.9 ppm.

High dose-related early mortality occurred in both groups of treated male rats (NCI, 1978). Ten low-dose males survived past week 80 and were sacrificed in week 82. Six high-dose males survived past week 71 and were sacrificed in week 74. Histopathological effects of treatment in rats included high incidences of toxic nephropathy in both sexes and testicular atrophy in males. These effects occurred at both dosage levels and appeared to be dose-related. The survival of the female rats was not affected by treatment.

High early mortality, starting at week 19, occurred among treated male mice and appeared to be dose-related, but the association between increased dosage and elevated mortality was not significant according to NCI (1978). The data are difficult to interpret because of high mortality among the male control mice (11/20 died at week 72, possibly because of fighting). Survival of the male mice at the end of the experiment was 15% for controls, 28% for the low-dose and 10% for the high-dose group. NCI (1978) concluded that deaths among the high dose male mice were not attributable to a "common cause" and that no specific histopathological lesions, including toxic nephropathy, occurred at higher incidences in treated males than in control males. U.S. EPA (1980a), however, reported that endosulfan treatment was toxic to the kidneys of male mice in the NCI (1978) bioassay. Inspection of the NCI (1978) data reveals an increased incidence of hydronephrosis in low-dose male mice, but not in high-dose male mice or in female mice; none of the mice had toxic nephropathy. NCI (1978) did not discuss the finding of

hydronephrosis in low-dose male mice. Survival and incidences of histopathological lesions in female mice were not affected by treatment.

Other than the NCI (1978) bioassay, the only studies concerning chronic endosulfan toxicity are an unpublished rat study (Keller, 1959b), discussed briefly in ACGIH (1986), Maier-Bode (1968) and U.S. EPA (1982), and a carcinogenicity study in mice (BRL, 1968). In the Keller (1959b) study, groups of 25 male and 25 female Wistar rats were fed diets containing 0, 10, 30 or 100 ppm technical grade endosulfan for 2 years. General appearance, behavior, food consumption or hematological parameters were not affected. Survival of high-dose females was significantly reduced. High-dose males exhibited slight to moderate growth depression and increased relative kidney weights. Histopathological effects consisting of renal tubule dilatation, formation of albuminous casts, focal interstitial nephritis and degeneration of tubule epiethelium occurred in the kidneys and hydropic cells with pale eosinophilic cytoplasmic inclusions occurred in the livers of high-dose males. The results of this study indicated that a dietary concentration of 30 ppm (1.5 mg/kg/day) was a NOEL. U.S. EPA (1982), however, concluded that this study was an inadequate evaluation of chronic toxicity because the number of animals surviving 2 years and the number of animals examined were limited and because of the lack of blood and urine chemistry analyses.

In the BRL (1968) study, survival in one or both sexes of two strains of mice treated by gavage with 1.0 or 2.15 ppm technical grade endosulfan in gelatin from 7-28 days of age and subsequently with 3 or 6 ppm, respectively, in the diet for ~18 months was very poor compared with gelatin-treated controls. Survival after 18 months was 16/18, 9/18 and 1/18 in the control, low-dose and high-dose B6C3F1 males, respectively; 18/18, 9/18 and 1/18 in the B6C3F1 females; 18/18, 16/18 and 6/18 in the B6AKF1 males; and 15/18,

12/18 and 8/18 in the B6AKF1 females. Decreased survival was not due to tumors, but any additional information regarding toxicity was not reported since this study was designed primarily to investigate carcinogenicity.

3.2.2. Inhalation. Pertinent data regarding the toxic effects of chronic inhalation exposure to endosulfan were not located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Teratogenicity of endosulfan has not been demonstrated in oral studies with rats and rabbits. Fetotoxic effects occurred, but only at dosages that produced maternal toxicity.

Gupta et al. (1978) administered 0, 5 or 10 mg/kg endosulfan by gavage to groups of 20-32 albino rats on days 6-14 of gestation. Markedly increased numbers of resorptions and a dose-related increase in maternal mortality occurred in the treated rats, but gross abnormalities were not observed in the fetuses.

In an unpublished teratogenicity study (Raltech Scientific Services, 1980) conducted with rats, adverse effects on the fetus were noted at 6 mg/kg. These effects included reduced size and weight, and skeletal, visceral and external anomalies. The dams, however, had decreased body weights and signs of CNS stimulation. The NOEL for fetotoxicity was 2 mg/kg. No other details, including the route of administration, were provided in the U.S. EPA (1982) summary of this study.

U.S. EPA (1982) also described another unpublished study (Raltech Scientific Services, 1982) in which groups of pregnant rabbits received oral dosages of 0.3, 0.7 or 1.8 mg/kg/day on days 6-28 of gestation. Maternal toxicity was apparent in the high-dose group; effects included hyperactivity, rapid breathing, convulsions and death. No treatment-related effects

in number of corpora lutea, implantation efficiency, litter size, sex ratio of offspring, mean fetal length, fetal weight or numbers of live and resorbed fetuses were observed; however, "common skeletal variations and anomalies" (unspecified) occurred in all groups. U.S. EPA (1982) did not clarify if a control group was used in this study but concluded that a NOEL for maternal toxicity of 0.7 mg/kg/day was defined.

Dose-related testicular atrophy occurred in rats that were treated with 408 or 952 ppm (TWA) endosulfan in the diet for up to 82 weeks (NCI, 1978). Vettorazzi (1975) mentioned a 3-generation rat study in which 50 ppm endosulfan in the diet had no effect on reproduction or survival, but no details were provided.

In an unpublished 2-generation reproduction study in the rat (Huntingdon Research Centre, 1984), exposure with dietary levels of 0, 3, 15 and 75 ppm endosulfan produced litter loss in the F_0 at both matings at 3 and 15 ppm levels. At 75 ppm the effect was comparable with the control. In the F_{1b} generation there was a compound-related increase in litter loss over controls at both matings. There were no dose-related or compound-related effects on reproductive performance, except for decreased litter weight at 75 ppm in the F_{1a} and F_{1b} litters. Teratological events were also not observed in any of the dosages tested in the above study. Interestingly, however, yellowish discoloration of the cells of the proximal convoluted tubules of the kidney was found in traces in F_{1b} males at all doses, and in minimal amounts in males at 75 ppm only. In addition, granular clumped pigment was observed in trace amounts in these cells; suggesting some destructions of red blood cells in the hematopoietic system occurring at all doses tested in males. Therefore, the lowest dose, 3 ppm endosulfan or 0.15 mg/kg/day (based on food consumption at the rate of 5% g bw), represents a LOAEL.

3.3.2. Inhalation. Pertinent data regarding the reproductive and developmental toxicity of endosulfan by inhalation exposure were not located in the available literature.

3.4. TOXICANT INTERACTIONS

Two human fatalities involved endosulfan ingested with alcohol, although dimethoate was also used in one formulation (Demeter and Heyndrickx, 1978). Increased gastrointestinal absorption of endosulfan in the presence of alcohols has been reported (Lendle, 1956). These data were interpreted as suggesting that synergism between alcohol and endosulfan is likely (Demeter and Heyndrickx, 1978).

Dose-dependent increased activities of aminopyrine-N-demethylase and aniline hydroxylase in endosulfan-treated rats suggest that endosulfan is an inducer of the mixed-function oxidase system (Agarwal et al., 1978).

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenicity of endosulfan to humans exposed orally or by inhalation were not located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. An NCI (1978) bioassay of endosulfan provided no evidence that endosulfan is carcinogenic. This assay was conducted with rats and mice that were exposed in the diet. High early mortality occurred in the males of both species, apparently because of toxic nephropathy in the rats (see Section 3.2.1.). Significant increases in the incidence of tumors at any site did not occur among dosed rats or mice of either sex. No conclusions regarding the carcinogenicity of endosulfan in the male rats or mice could be drawn because the shortened lifespans precluded evaluation of the occurrence of late-developing tumors. In a review of this study, U.S. EPA (1980a) concluded that the NCI (1981) bioassay was a stringent test for carcinogenicity and that the negative results were valid. Reuber (1981) re-examined histological sections from this study and concluded that endosulfan was carcinogenic, although no dose-related trends in the incidence of any particular type of tumor were found.

Endosulfan was also tested for carcinogenicity in mice by BRL (1968). Thiodan, a 96% pure mixture of endosulfan isomers, was administered to B6C3F1 and B6AKF1 strains of mice by stomach tube at 1 or 2.15 mg/kg/day in gelatin from days 7-28 of age to ~18 months, followed by administration in the diet at concentrations of 3 and 6 ppm, respectively. Both treatment groups consisted of 18 male and 18 female mice of each strain. BRL (1968) concluded that there was a statistically significant ($p=0.05$) increase relative to controls in the incidences of pulmonary adenomas and total

tumors in mice treated orally with endosulfan. The incidences in both strains, sexes and dose groups were pooled in this analysis; however, in a summary of the data and results of this study, Innes et al. (1967) classified endosulfan as a compound "which did not cause a significant increase in tumors after oral administration." U.S. EPA (1980a) did not address this apparent discrepancy explicitly, but instead reported the conclusions of Innes et al. (1967) and relied heavily upon the more recent NCI (1978) bioassay to evaluate the possible carcinogenicity of endosulfan.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of endosulfan by inhalation were not located in the available literature.

4.3. OTHER RELEVANT DATA

Endosulfan has yielded mixed results in various mutagenicity assays using Salmonella typhimurium (Dorough et al., 1978; U.S. EPA, 1980a), while negative results were obtained in Saccharomyces cerevisiae, Escherichia coli and Serratia marcescens (U.S. EPA, 1980a). Endosulfan was mutagenic in Drosophila melanogaster in the sex-linked recessive lethal and sex-chromosome loss tests (Velazquez et al., 1984). In mice fed endosulfan (43.3 mg/kg), there was no significant increase in the frequency of polychromatic erythrocytes with micronuclei (Rani et al., 1980); however, endosulfan produced a significant increase in frequency of sister chromatid exchanges in cultured human lymphoid cells (Sobti et al., 1983).

BRL (1968) administered a 2.15 mg/kg dose of endosulfan in DMSO to groups of 18 male and 18 female 28-day-old B6C3F1 and B6AKF1 mice by subcutaneous injection. The mice were sacrificed after an 18-month observation period and examined for pulmonary adenomas. The incidence of adenomas in treated rats did not differ significantly from that in controls.

4.4. WEIGHT OF EVIDENCE

Endosulfan has been tested for carcinogenicity in rats (NCI, 1978) and mice (NCI, 1978; BRL, 1968; Innes et al., 1967) in chronic oral studies with negative and inconclusive results. U.S. EPA (1980a) concluded that endosulfan was not carcinogenic. Given the inconclusiveness of one NCI bioassay and the difference of opinion about the BRL assay, the criteria for two clearly negative studies is not met and the animal data base is judged to be inadequate. Endosulfan is, therefore, most appropriately classified in EPA Group D (U.S. EPA, 1986c).

5. REGULATORY STANDARDS AND CRITERIA

U.S. EPA (1980a) derived an RfD for endosulfan of 0.028 mg/day for a 70 kg human from the low dietary concentration (2 ppm) in the NCI (1978) study in mice. This RfD was used as the basis for an ambient water quality criterion of 75 µg/ℓ. The FAO/WHO (Vettorazzi, 1975) has adopted an RfD of 0.0075 mg/kg/day for α- and β-endosulfan and endosulfan sulfate, based on the NOEL of 0.75 mg/kg/day in dogs exposed 6 days/week for 1 year (Keller, 1959a).

ACGIH (1986) currently recommends a TLV-TWA of 0.1 µg/m³ for occupational atmospheric exposure to endosulfan.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). NCI (1978) conducted 6-week range-finding studies with groups of five male and five female B6C3F1 mice that were exposed to 0, 3.2, 5.6, 10, 18 or 32 ppm endosulfan in the diet and to Osborne-Mendel rats that were similarly exposed to 0, 178, 316, 562, 1000 or 1780 ppm. Body weight depression and mortality occurred in the mice at $\geq$5.6 ppm (see Section 3.1.1.). In the rats, body weight depression occurred in the males at $\geq$562 ppm, but was not observed in the females, and deaths occurred at 1780 ppm in the males and at 316 and 562 ppm in the females. The mouse and rat NOELs (3.2 and 178 ppm, respectively) correspond to 0.4 and 8.9 mg/kg/day dosages (see Section 3.1.1.).

Other subchronic oral toxicity studies have been conducted with rats that were exposed to endosulfan for 7-60 days (see Sections 3.1.1. and 3.3.1.). The Huntingdon Research Centre study (1984) reported yellowish discoloration of cells along with clumped pigments in trace amounts in these cells of the proximal convoluted tubules of kidneys of males exposed at all dosages tested (3, 15 and 75 ppm). The lowest dose, 3 ppm endosulfan or 0.15 mg/kg/day in males, represents a LOAEL.

Dogs that were exposed to endosulfan in capsules at doses of 0.075, 0.25 or 0.75 mg/kg/day, 6 days/week for 1 year showed no treatment-related effects on growth, organ weights, biochemical/hematological/urine chemistry parameters or gross histopathology (Keller, 1959a; Baran, 1967) (see Section 3.1.1.).

The LOAEL of 0.15 mg/kg/day from the Huntingdon Research Centre (1984) rat study is the most appropriate basis for calculation of an RfD_{SO} for endosulfan because rats appear to be the most sensitive species and the

lowest adverse effect level (0.15 mg/kg/day, corresponding to 3 ppm in the diet) is below the NOELs in the rat and mice studies (see Section 3.1.1.). The high- est NOEL from the dog studies (0.75 mg/kg/day) (Keller, 1959a; Baran, 1967) is supportive of the mouse 0.4 mg/kg/day NOEL, but less well defined, because of a shortage of LOEL data. Using the rat LOAEL of 0.15 mg/kg/day with an uncertainty factor of 1000 results in an RfD_{SO} of 0.00015 mg/kg/day, or 0.01 mg/day for a 70 kg man.

The CBI literature contains a 13-week diet study that defines a LOAEL of 10 ppm for rats (0.64 mg/kg/day for males and 0.75 mg/kg/day for females, using reported food consumption and body weight data) for hematological effects. The LOAEL of 0.15 mg/kg/day for rats (Huntingdon Research Centre, 1984) is comparable with the LOAEL for hematological effects in the CBI; the recommended RfD_{SO} is appropriate as calculated.

6.1.2. Inhalation (RfD_{SI}). The lack of pertinent inhalation toxicity data for endosulfan precludes calculation of an RfD_{SI}.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). An RfD_0 of 0.004 mg/kg/day was calculated for endosulfan from the chronic diet NOEL of 2 ppm for female mice in the NCI (1978) bioassay with an uncertainty factor of 100 (U.S. EPA, 1980a). It appears that the higher NOEL of 3.9 ppm in the female mice was not used as the basis for the RfD because this is above the low dose for male mice (3.5 ppm) that was associated with nephrotoxicity (U.S. EPA, 1980a). In the calculation of the RfD, the 2 ppm NOEL was converted to a daily dosage of 0.4 mg/kg/day by assuming that a mouse consumes an amount of food equivalent to 20% of its body weight (5 g food/25 g body weight) daily (U.S. EPA, 1980a). Current methodology, however, assumes that a mouse consumes an amount of food equivalent to 13% of its body weight/day (U.S. EPA, 1980b).

Application of this food factor (0.13) to the dietary level of 2 ppm results in a dosage of 0.26 mg/kg/day, which corresponds to an RfD of 0.0026 mg/kg/day when an uncertainty factor of 100 is used. However, the 2-generation rat study (Huntingdon Research Centre, 1984) provided LOAEL for nephrotoxicity possibly resulting from hematopoietic effects in male rats exposed to 0.15 mg/kg/day. It would be therefore appropriate to apply an uncertainty factor of 10,000 to this LOAEL to derive an RfD_0 of 0.000015 mg/kg/day for endosulfan. This number was derived by the Office of Pesticide Programs (OPP) and verified by the Agency-wide RfD committee on June 11, 1986 (U.S. EPA, 1986a).

The OPP previously reported a provisional RfD of 0.0075 mg/kg/day based on a 1-year oral dog NOEL of 0.750 mg/kg/day (U.S. EPA, 1982). This RfD is identical to that adopted by the FAO/WHO (Vettorazzi, 1975). The dog NOEL is not an appropriate basis for an RfD because it is higher than the dosage of endosulfan (NCI, 1978) that appeared to be associated with early mortality and hydronephrosis in male mice (i.e., 3.5 ppm in the diet, which is equivalent to 0.46 mg/kg/day when a food factor of 0.13 is applied) and is very close to the dosage (BRL, 1968) associated with increased mortality in both male and female mice (6 ppm in the diet, which is equivalent to 0.78 mg/kg/day). In addition, the mice were treated for nearly the entire lifespan, whereas the dogs were treated for considerably less than their lifespans.

CSs for endosulfan can be calculated from the NCI (1978), BRL (1968) and Keller (1959b) chronic oral bioassays conducted with rats and mice (see Section 3.2.1.). Treatment-related mortality that was not attributed to tumor development occurred at all dosages that produced effects in those studies. The derivations of CSs from the lowest dosages producing mortality in these studies are presented in Table 6-1. Mortality in mice from the

TABLE 6-1

Composite Scores for the Toxicity of Endosulfan by Oral Exposure

Species/Strain	Sex	Exposure Dosage (mg/kg/day)	Human MED (mg/day)	RV_d	Effect	RV_e	CS	Reference
Rat/Osborne-Mendel	M	20.4 for 82 weeks[a]	275[a]	1.8	mortality	10	18	NCI, 1978
Rat/Wistar	M	5.0 for 2 years[b]	59.8[b]	2.8	mortality	10	28	Keller, 1959b
Mouse/B6C3F1	M or F	0.4 for 77 weeks[c]	2.3[c]	5.0	mortality	10	50	BRL, 1968
Rat/albino	F	5 on days 6-14 of gestation[d]	48.8	3.0	fetotoxicity (resorptions)	8	24	Gupta et al., 1978
Rat/Crl: COBSCD(SD)BR		0.15 over 2 generations	1.8	5.0	nephrotoxicity	5	25	Huntingdon Research Centre, 1984

[a]408 ppm in the diet. Assumed the equivalent of 5% of body weight consumed/day in food (U.S. EPA, 1980b). Average measured rat body weight is ~0.5 kg.

[b]100 ppm in the diet. Assumed the equivalent of 5% of body weight consumed/day in food (U.S. EPA, 1980b). Average rat body weight assumed to be 0.35 kg.

[c]1.0 mg/kg/day by gavage for 28 days followed by 3 ppm in the diet for 73 weeks. TWA dosage calculated with the assumption that mice consume food equivalent to 13% of body weight/day (U.S. EPA, 1980b).

[d]Reported body weight is 0.19 kg.

NCI (1978) study was not used as an endpoint because it was not definitely attributed to treatment. Fetotoxicity in the Gupta et al. (1978) study (see Section 3.3.1.) is also an appropriate basis for a CS calculation for endosulfan.

Standard chronic toxicity RQ methodology was used to calculate the CSs. This involved using standard food consumption estimates to convert dietary exposure into mg/kg/day dosages and assumed or reported body weights and the cube root of the body weight ratio approximation to convert the animal MEDs to human MEDs (see Table 6-1). RV_es of 10 and 8 most appropriately reflect the mortality and fetotoxicity, respectively. The highest CS (50) is calculated from the mortality in mice (BRL, 1968), reflecting the greater susceptibility of mice compared with other test species to endosulfan.

6.2.2. Inhalation (RfD_I). The lack of pertinent inhalation toxicity data for endosulfan precludes calculation of an RfD_I or CS.

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values amd Biological Exposure Indices, 5th ed. Cincinnati, OH. p. 230.

Agarwal, D.K., et al. 1978. Effect of endosulfan on drug metabolizing enzymes and lipid peroxidation in rat. J. Environ. Sci. Health. C13: 49. (Cited in U.S. EPA, 1980a)

Ansari, R.A., M.K.J. Siddiqui and P.K. Gupta. 1984. Toxicity of endosulfan: Distribution of α- and B-isomers of racemic endosulfan following oral administration in rats. Toxicol. Lett. 21(1): 29-33. (CA 101:2028t)

Baran, J. 1967. Report to Niagara Chemical Division, FMC Corporation: Two-year chronic oral toxicity of thiodan technical - beagle dogs: IBT No. C3758. (Unpublished study including letter dated Dec. 5, 1967 from J.C. Calandra to John F. McCarthy, received Dec. 7, 1967 under 7F0632; prepared by Industrial Bio-Test Laboratories, Inc., submitted by FMC Corp., Philadelphia, PA. CDL:091100-A) MRID 00003741.

BRL (Bionetics Research Labs, Inc.) 1968. Evaluation of carcinogenic, teratogenic and mutagenic activities of selected pesticides and industrial chemicals. Vol. 1. Carcinogenic study. National Cancer Institute. NTIS PB 223-159.

Callahan, M.A., M.W. Slimak, N.W. Gabel, I.P. May, C.F. Fowler and J.R. Feed. 1979. Water-related environmental fate of 129 priority pollutants - Vol. I. U.S. EPA, Washington, DC. EPA 440/4-79-029B.

Czech, M. 1958. No title provided. Medicin v. Chemie. 6: 574. (Cited in ACGIH, 1986)

Demeter, J. and A. Heyndrickx. 1978. Two lethal endosulfan poisonings in man. J. Anal. Toxicol. 2: 68. (Cited in U.S. EPA, 1980a)

Den Tonkelaar, E.M. and C.J. Van Esch. 1974. No-effect levels of organochlorine pesticides based on induction of microsomal liver enzymes in short-term toxicity experiments. Toxicology. 2: 371-380.

Dikshith, T.S.S., R.B. Raizada, M.K. Srivastava and B.S. Kaphalia. 1984. Response of rats to repeated oral administration of endosulfan. Ind. Health. 22(4): 295-304. (CA 102:107828c)

Dorough, H.W., K. Huhtunen, T.C. Marshall and H.E. Bryant. 1978. Fate of endosulfan in rats and toxicological considerations of apolar metabolites. Pestic. Biochem. Physiol. 8: 241-252.

Gupta, P.K. and R.C. Gupta. 1977. Effect of endosulfan pretreatment on organ weights and on pentobarbitol hypnosis in rats. Toxicology. 7: 283-288.

Gupta, P.K., S.V. Chandra and D.K. Saxena 1978. Teratogenic and embryotoxic effects of endosulfan in rats. Acta Pharmacol. Toxicol. 42: 150-152.

Hansch, C. and A.T. Leo. 1985. Medchem Project Issue No. 26. Pomona College, Claremont, CA.

Huntingdon Research Centre. 1984. Effect of Endosulfan-Technical on Reproductive Function of Multiple Generations in the Rat. Report submitted by J.A. Edwards et al. to the Office of Pesticides Program, U.S. EPA.

Innes, J.R.M, B.M. Ulland, M.G. Valerio, et al. 1967. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice. A preliminary note. J. Natl. Cancer Inst. 42: 1101-1114.

Keller, J.G. 1959a. Final report: Repeated oral administration - dogs. (Unpublished study received Feb. 9, 1960, under PP0237; Prepared by Hazleton Laboratories, Inc. FMC Corp. Philadelphia, PA. CDL:090365H) MRID 00003604. (Cited in U.S. EPA, 1982)

Keller, J.G. 1959b. Final report: Two-year chronic feeding study - rats: (thiodan technical). (Unpublished study received Feb. 9, 1960, under PP0237; Prepared by Hazleton Laboratories, Inc. FMC Corp., Philadelphia, PA. CDL:090265-E) MRID 00003602. (Cited in U.S. EPA, 1982)

Lendle, L. 1956. Bericht uber Untersuchungen von Hoe 2671 (Thiodan) der Farbwerke Hoechst A.G., July 1956. In: Maier-Bode, 1968. (Ger.) (Cited in U.S. EPA, 1980a)

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. McGraw-Hill, New York. p. 4-9.

Maier-Dode, H. 1968. Properties, effect, residues, and analytics of the insecticide endosulfan (review). Residue Rev. 22: 2-44. (Cited in U.S. EPA, 1980a)

NCI (National Cancer Institute). 1978. Bioassay of endosulfan for possible carcinogenicity. NCI Carcinogenesis. Tech. Rep. Ser. No. 62. 54 p. [Also publ. as DHEW (NIH) 78-1312]

Raltech Scientific Services. 1980. Final report: Teratology study with FMC 5462 in rats: Raltech Study No. 79041. (Unpublished study received Nov. 12, 1980 under 279-2306: FMC Corp., Philadelphia, PA. CDL:243707) MRID GS014008. (Cited in U.S. EPA, 1982)

Raltech Scientific Services. 1982. Final report: Teratology study with FMC 5462 in rabbits: Raltech Study No. 80070. (Unpublished study received Feb. 16, 1982, under 279-2306; FMC Corp., Philadelphia, PA. CDL:246792) MRID GS014023. (Cited in U.S. EPA, 1982)

Rani, M.V.U., O.S. Reddi and P.P. Reddy. 1980. Mutagenicity studies involving aldrin, endosulfan, dimethoate, phosphamidon, carbaryl and ceresan. Bull. Environ. Contam. Toxicol. 25(2): 277-82. (CA 93:198808f)

Reuber, M.D. 1981. The role of toxicity in the carcinogenicity of endosulfan. Sci. Total Environ. 20(1): 23-47.

Sanborn, J.R., B.M. Francis and R.L. Metcalf. 1977. The degradation of selected pesticides in soil: A review of the published literature. Office of Research and Development, U.S. EPA, Cincinnati, OH. EPA 600/9-77-02. p. 339-342.

Singh, N.C., T.P. Dasgupta, E.V. Roberts and A. Nansingh. 1986. Kinetics of hydrolysis of endosulfan and vamidothion. In: ACS Nat. Meet. Div. Agrochemicals, New York.

Sobti, R.C., A. Krishan and J. Davies. 1983. Cytokinetic and cytogenetic effect of agricultural chemicals on human lymphoid cells in vitro. II. Organochlorine pesticides. Arch. Toxicol. 52: 221-231.

U.S. EPA. 1980a. Ambient Water Quality Criteria for Endosulfan. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-046. NTIS P881-117574.

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 79347-79357.

U.S. EPA. 1982. Hexachlorohexahydromethano-2,4,3-benzodioxathiepin 3-oxide (Endosulfan) Pesticide Registration Standard. Office of Pesticides and Toxic Substances, U.S. EPA, Washington, DC. April, 1982. NTIS P882-243999.

U.S. EPA. 1983. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmnetal Criteria and Assessment Office, U.S. EPA, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986a. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Endosulfan. Online (verification date 6/11/86; data input pending). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1986b. Reference Values for Risk Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1986c. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

Velazquez, A., A. Creus, N. Xamena and R. Marcos. 1984. Mutagenicity of the insecticide endosulfan in Drosophila melanogaster. Mutat. Res. 136(2): 115-18. (CA 101:18845t)

Vettorazzi, G. 1975. State of the art of the toxicological evaluation carried out by the Joint FAO/WHO Expert Committee on Pesticide Residues. I. Organohalogenated pesticides used in public health and agriculture. Residue Rev. 56: 107-134.

Worthing, C.R. 1983. The Pesticide Manual, 7th ed. The British Crop Protection Council. p. 233.

APPENDIX

Summary Table for Endosulfan

	Species	Experimental Exposure/Dose (mg/kg/day)	Effect	Reference Dose (RfD or RfD_S)	Reference
Inhalation					
RfD_{SI} (formerly AIS)		not calculated because of lack of data			
RfD_I (formerly AIC)		not calculated because of lack of data			
Oral					
RfD_{SO}	rat	0.15 mg/kg/day in the diet 2-generation reproduction study	LOAEL	0.01 mg/day	Huntington, Research Center, 1984
RfD_O	rat	0.15 mg/kg/day in the diet 2-generation reproduction study	LOAEL	0.001 mg/day	Huntington, Research Center, 1984
Maximum					
CS		1 mg/kg/day by gavage for 28 days followed by 3 ppm in the diet for 73 weeks (0.4 mg/kg/day TWA) (RV_d = 50)	mortality (RV_e = 10)	CS = 50	BRL, 1968